

Study Title
COMBINED CHRONIC TOXICITY/ONCOGENICITY
STUDY 2-YEAR ORAL GAVAGE STUDY IN RATS

Laboratory Project ID:

Volume 11 of 13

NUMBER OF PAGES IN VOLUME: 351

- TEST GUIDELINES:**
- U.S. EPA Health Effects Test Guidelines OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity (1998)
 - OECD Guidelines for the Testing of Chemicals Section 4 (No. 453) Health Effects (2009)
 - JMAFF Japan Agricultural Chemicals Regulation Law 12 Nousan No. 8147 (2000)
 - EEC Methods for the Determination of Toxicity Method B.33 Combined Chronic/Carcinogenicity test, Directive 88/302/EC (1988)

AUTHOR:

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APPLICANT/SPONSOR:

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PERFORMING LABORATORY:

WORK REQUEST NUMBER:

SERVICE CODE NUMBER:

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1415	D	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular	- within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1415	D	Microscopic thymus	- depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1416	S	Macroscopic lymph node, axillary	- within normal limits draining node for mass a, left. draining node for mass b, right.
		mammary gland	- swollen/thickened, tan, generalized, mild
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1416	S	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 5.0 cm in diameter. - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (nodule) approximately 1.2 cm in diameter.
1416	S	Microscopic adrenal glands kidneys liver lung lymph node, axillary	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - vacuolation, periportal, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1416	S	Microscopic mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened)
1417	D	pancreas stomach, nonglandular tongue uterus with cervix	<ul style="list-style-type: none"> - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild
		Macroscopic lymph node, inguinal	<ul style="list-style-type: none"> - not identified, bilateral, no grade draining node for mass a, c, and d, left. draining node for mass b, right.
		pituitary gland	<ul style="list-style-type: none"> - enlarged, red, moderate
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1417	D	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 5.0 cm in diameter. - mass, tan, mass b, right inguinal area, present corresponds to antemortem observation (mass 2) approximately 3.5 cm in diameter. - mass, tan, mass c, anogenital region, present corresponds to antemortem observation (nodule) approximately 2.3 cm in diameter. - mass, tan, mass d, left inguinal area, present approximately 1.4 x 1.2 x 2.6 cm.
1417	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

D - Died on Study

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Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1417	D	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, moderate - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1417	D	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c; skin, subcutis - mass d) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal - within normal limits - within normal limits - not examined - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1417	D	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1417	D	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - pituitary tumor
1418	S	Macroscopic lymph node, mandibular pituitary gland skin, subcutis	- within normal limits draining node for mass a, left. - cyst, red, mild - mass, tan, mass a, ventral neck, present corresponds to antemortem observation (mass 1) approximately 4.5 x 4.0 x 2.0 cm.
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1418	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		kidneys	- hyperplasia, focal cortical, unilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal
		liver	- nephropathy, chronic progressive, bilateral, minimal - focus of cellular alteration, basophilic, mild - focus of cellular alteration, eosinophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		pancreas	- atrophy, acinar, minimal
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - cyst)
		stomach, nonglandular	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1418	S	Microscopic tongue uterus with cervix	- within normal limits - within normal limits
1419	S	Macroscopic lymph node, axillary lymph node, inguinal pituitary gland	- within normal limits draining node for mass f and mass g, right. - not identified, bilateral, no grade draining node for mass a and b, left, and mass c, d, and e, right. - enlarged, moderate
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1419	S	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, green, mass b, left inguinal area, present approximately 4.0 x 3.0 x 1.5 cm. - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 1.0 x 9.0 x 3.5 cm. - mass, tan, mass c, right inguinal area, present approximately 2.0 cm in diameter. - mass, tan, mass d, right inguinal area, present approximately 2.5 cm in diameter. - mass, tan, mass e, right inguinal area, present approximately 1.5 cm in diameter. - mass, tan, mass f, right axillary area, present corresponds to antemortem observation (swelling) approximately 5.0 x 3.5 x 2.0 cm. - mass, tan, mass g, right axillary area, present corresponds to antemortem observation (nodule) approximately 4.0 x 2.0 x 1.0 cm. - prolapse, moderate
1419	S	vagina Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1419	S	Microscopic kidneys liver lung lymph node, axillary	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1419	S	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass d; skin, subcutis - mass e; skin, subcutis - mass g)
		pancreas	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c; skin, subcutis - mass f)
		pituitary gland	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- polyp, stromal, benign, primary, incidental, not cause of death corresponds to macroscopic observation (vagina - prolapse)
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1420	D	Macroscopic eyes	- absent, left, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		eyes, retina	- absent/cannibalized, left, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		lacrimal glands, exorbital	- absent/cannibalized, left, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		lymph node, mandibular	- absent/cannibalized, left, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		salivary gland, mandibular	- absent/cannibalized, bilateral, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		salivary gland, parotid	- absent/cannibalized, left, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		salivary gland, sublingual	- absent/cannibalized, bilateral, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1420	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate - vacuolation, focal, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits one of pair present
		eyes, optic nerves	- within normal limits
		eyes, retina	- not examined autolysis too severe for diagnosis
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1420	D	Microscopic kidneys	- mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits one of pair present
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hyperplasia, bile duct, minimal
		lung	- within normal limits
		lymph node, mandibular	- not examined
		lymph node, mesenteric	- within normal limits
		mammary gland	- within normal limits
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1420	D	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - not examined cannibalized - within normal limits - not examined cannibalized - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1420	D	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - undetermined
1421	E	Macroscopic lymph node, axillary mammary gland	- enlarged, right, mild draining node for mass a. - swollen/thickened, tan, anogenital region, mild

E - Euthanized *in extremis*

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1421	E	Macroscopic pituitary gland skin, subcutis	- enlarged, minimal - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 2.5 cm in diameter, red.
1421	E	spleen Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- enlarged, mild - angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1421	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, mild - within normal limits - hyperplasia, lymphocyte/plasmacyte, medulla, mild corresponds to macroscopic observation (lymph node, axillary - enlarged) - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1421	E	Microscopic mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - galactoceles, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened)
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1421	E	Microscopic pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild corresponds to macroscopic observation (spleen - enlarged) - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1421	E	Microscopic tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary gland - enlarged - mammary tumor
1422	E	Macroscopic ovaries pituitary gland	- cyst, clear, right, mild - enlarged, severe
1422	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1422	E	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	 - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1422	E	Microscopic liver	- degeneration, cystic, focal, minimal - infiltration, mononuclear cell, minimal
		lung	- within normal limits
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, mild
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
			one of pair present
		pharynx	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1422	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1422	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - ovaries - cyst - pituitary tumor
1423	E	Macroscopic pituitary gland	- enlarged, severe
1423	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1423	E	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1423	E	Microscopic lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1423	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1423	E	Microscopic ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits one of pair present - within normal limits - within normal limits - within normal limits - pituitary tumor
1424	S	Macroscopic mammary gland pituitary gland	- swollen/thickened, mild anogenital, right and left inguinal mostly affected. - enlarged, red, severe
1424	S	Microscopic adrenal glands kidneys liver	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - mineralization, pelvic, bilateral, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1424	S	Microscopic lung mammary gland pancreas pituitary gland stomach, nonglandular tongue uterus with cervix	- within normal limits - galactoceles, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - atrophy, acinar, minimal - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - dilatation, gland/lumen, minimal
1425	S	Macroscopic adipose tissue	- discoloration, yellow, mild in white fat near left kidney.
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1425	S	Macroscopic lymph node, inguinal	- within normal limits draining node for mass a, left.
		skin, subcutis	- mass, tan, mass a, left inguinal area, present approximately 2.0 cm in diameter.
1425	S	thymus	- small, mild
		Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		kidneys	- hyperplasia, focal cortical, unilateral, minimal - mineralization, pelvic, unilateral, minimal - mineralization, tubular, unilateral, minimal
		liver	- nephropathy, chronic progressive, bilateral, mild - focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, mild
		lung	- vacuolation, periportal, minimal
		lymph node, inguinal	- within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1425	S	Microscopic mammary gland mesentery/peritoneum pancreas stomach, nonglandular thymus tongue uterus with cervix	- fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a) - necrosis, fat, moderate corresponds to macroscopic observation (adipose tissue - discoloration, yellow) - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate corresponds to macroscopic observation (thymus - small) - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, cervical fibromuscular, mild
1426	E	Macroscopic lymph node, axillary	- within normal limits right is draining node for mass c. left is draining node for mass a.

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1426	E	Macroscopic lymph node, inguinal ovaries with oviducts pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits left is draining node for mass b. - cyst, clear, left, mild - enlarged, red, severe - mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 3.0 x 2.5 x 1.7 cm. - mass, tan, mass b, left anogenital region, present corresponds to antemortem observation (mass 2) approximately 5.0 x 4.0 x 2.5 cm. - mass, tan, mass c, right axillary area, present corresponds to antemortem observation (nodule) approximately 2.0 x 1.5 x 0.7 cm
1426	E	Microscopic adrenal glands aorta bone marrow, femur	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, bilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1426	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	- within normal limits - within normal limits - within normal limits - carcinoma, pars distalis, malignant, secondary - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1426	E	Microscopic larynx liver lung lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a	- within normal limits - hyperplasia, bile duct, minimal - foreign material, mild plant. - inflammation, acute, moderate - within normal limits - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass c) - hyperplasia, lobular, mild - within normal limits - exudate, nasal passage, mild - foreign material, minimal plant.

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1426	E	Microscopic nose, level b	- exudate, nasal passage, mild - foreign material, mild plant.
		nose, level c	- exudate, nasal passage, minimal - foreign material, minimal plant.
		nose, level d	- exudate, nasal passage, mild - foreign material, mild plant.
		ovaries	- cyst, unilateral, mild corresponds to macroscopic observation (ovaries with oviducts - cyst)
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- carcinoma, pars distalis, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1426	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, mild - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1426	E	Microscopic urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - pituitary tumor
1427	D	Macroscopic pituitary gland	- enlarged, severe
1427	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal cortical, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1427	D	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1427	D	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - exudate, nasal passage, minimal - exudate, nasal passage, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1427	D	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1428	E	Macroscopic pituitary gland uterus with cervix	- enlarged, severe - enlarged, horn, mild
1428	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1428	E	Microscopic joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- within normal limits - hydronephrosis, unilateral, minimal - mineralization, pelvic, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death slide 18. - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1428	E	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1428	E	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - dilatation, unilateral, mild - within normal limits - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged) - within normal limits - pituitary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1429	S	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits draining node for mass b, right. draining node for mass c, left. - within normal limits draining node for mass a, bilateral. - enlarged, moderate - mass, tan, mass a, cervical, present corresponds to antemortem observation (mass 1) approximately 4.5 x 4.5 x 3.0 cm. - mass, tan, mass b, right anogenital region, present corresponds to antemortem observation (mass 2) approximately 6.0 x 5.0 x 2.0 cm. - mass, tan, mass c, left inguinal area, present corresponds to antemortem observation (mass 3) approximately 3.0 cm in diameter.
1429	S	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, unilateral, moderate
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1429	S	Microscopic kidneys	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
		liver	- focus of cellular alteration, basophilic, mild
		lung	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c)
		pancreas	- hyperplasia, acinar cell, focal, mild
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1430	S	Macroscopic adrenal glands lymph node, axillary lymph node, inguinal pituitary gland skin, subcutis	<ul style="list-style-type: none"> - enlarged, bilateral, mild - within normal limits - draining node for mass c, left. - enlarged, right, mild - draining node for mass a, mass b and mass d. - enlarged, red, mild - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 6.0 x 4.0 x 3.5 cm. - mass, tan, mass b, right inguinal area, present approximately 1.0 cm in diameter. - mass, tan, mass c, left axillary area, present corresponds to antemortem observation (nodule) approximately 2.0 x 1.0 x 1.0 cm. - mass, tan, mass d, right anogenital region, present corresponds to antemortem observation (nodule) approximately 2.5 x 2.0 x 1.5 cm.
1430	S	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild corresponds to macroscopic observation (adrenal glands - enlarged)
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1430	S	Microscopic kidneys liver lung lymph node, axillary lymph node, inguinal	- mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal - within normal limits - within normal limits - not examined misidentified tissue
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1430	S	Microscopic mammary gland	- adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (lymph node, inguinal - enlarged) slide 27-abd.
		pancreas	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c; skin, subcutis - mass d)
		pituitary gland	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1431	S	Macroscopic adrenal glands foot/feet lymph node, inguinal pituitary gland skin, subcutis	- enlarged, right, mild - ulcer, plantar/palmar, mild corresponds to antemortem observation (ulcer plantar/palmar) - within normal limits draining node for mass a, right. - enlarged, red, moderate - mass, tan, mass a, right anogenital region, present approximately 2.5 x 3.0 x 1.0 cm.
1431	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged) - hyperplasia, focal cortical, unilateral, mild - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1431	S	Microscopic kidneys	- mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		liver	- hyperplasia, bile duct, minimal - vacuolation, periportal, minimal
		lung	- within normal limits
		lymph node, inguinal	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a)
		pancreas	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1432	S	Macroscopic lymph node, iliac pituitary gland skin, subcutis	- within normal limits draining node for mass a, right. - enlarged, mild - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 4.0 cm in diameter.
1432	S	Microscopic adrenal glands kidneys liver lung lymph node, iliac	- hyperplasia, focal medullary, unilateral, mild - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, mild - degeneration, cystic, focal, minimal - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1432	S	Microscopic mammary gland pancreas pituitary gland stomach, nonglandular tongue uterus with cervix	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, acinar cell, focal, minimal - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - dilatation, gland/lumen, minimal
1433	E	Macroscopic pituitary gland skin	- enlarged, red, severe - hair sparse, dorsal cervical region, dorsal thoracic region, moderate corresponds to antemortem observation (hair sparse hair absent)
1433	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1433	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, bilateral, mild - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, mild - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1433	E	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- within normal limits - within normal limits - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - vacuolation, periportal, mild - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1433	E	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular	- within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1433	E	Microscopic stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - thymoma, malignant, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1434	S	Macroscopic lymph node, axillary lymph node, inguinal pituitary gland	- within normal limits draining node for mass c, right. - not identified, bilateral, no grade draining node for mass a, left and mass b, right. - enlarged, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1434	S	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1 mass 4) approximately 6.0 x 4.0 x 3.0 cm. - mass, tan, mass b, right inguinal area, present corresponds to antemortem observation (mass 2) approximately 6.0 x 3.5 x 3.0 cm. - mass, tan, mass c, right axillary area, present corresponds to antemortem observation (mass 3) approximately 3.0 cm in diameter.
1434	S	Microscopic adrenal glands kidneys liver lung lymph node, axillary	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1434	S	Microscopic mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c)
		pancreas	- atrophy, acinar, minimal
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- hyperplasia, squamous cell, minimal
1435	S	Macroscopic lymph node, axillary	- within normal limits draining node for mass b and mass d, right.
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1435	S	Macroscopic lymph node, inguinal ovaries pituitary gland skin, subcutis	<ul style="list-style-type: none"> - not identified, bilateral, no grade draining node for mass a, left and mass c, right. - cyst, clear, right, mild - enlarged, red, moderate - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 10.0 x 9.0 x 3.5 cm. - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (mass 2) approximately 2.5 cm in diameter. - mass, tan, mass c, right inguinal area, present corresponds to antemortem observation (mass 3) approximately 7.0 x 5.0 x 3.5 cm. - mass, tan, mass d, right axillary area, present corresponds to antemortem observation (mass 4) approximately 5.0 x 4.0 x 2.0 cm.
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1435	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death
		kidneys	- mineralization, pelvic, bilateral, minimal
		liver	- focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal
		lung	- histiocytosis, alveolar, minimal - inflammation, subacute/chronic, minimal
		lymph node, axillary mammary gland	- within normal limits - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c; skin, subcutis - mass d)
		ovaries	- cyst, unilateral, mild corresponds to macroscopic observation (ovaries - cyst)
		pancreas	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1435	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- cyst, keratin, minimal
		tongue	- within normal limits
		uterus with cervix	- hyperkeratosis, minimal - hyperplasia, squamous cell, minimal
1436	E	Macroscopic lung with bronchi	- discoloration, tan, multiple lobes, mild
		pituitary gland	- enlarged, red, severe
1436	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1436	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	- within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1436	E	Microscopic larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- within normal limits - focus of cellular alteration, basophilic, minimal - inflammation, acute, severe corresponds to macroscopic observation (lung with bronchi - discoloration, tan) plant material. - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1436	E	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular	- within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1436	E	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- not examined - within normal limits - within normal limits - inflammation, acute, minimal - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1437	S	Macroscopic adrenal glands lymph node, axillary lymph node, inguinal pituitary gland	- cyst, clear, left, mild - within normal limits draining node for mass a, right. - not identified, no grade draining node for mass c, bilateral and mass d, left. - enlarged, severe

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1437	S	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - abscess, right inguinal area, mild corresponds to antemortem observation (mass 2) - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 2.5 cm in diameter. - mass, tan, mass c, anogenital region, present corresponds to antemortem observation (nodule mass 3) approximately 3.0 cm in diameter. - mass, tan, mass d, left inguinal area, present approximately 2.0 cm in diameter.
1437	S	Microscopic adrenal glands kidneys liver lung	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - cyst) - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, mild - vacuolation, periportal, minimal - inflammation, subacute/chronic, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1437	S	Microscopic lymph node, axillary mammary gland pancreas pituitary gland stomach, nonglandular tongue uterus with cervix	<ul style="list-style-type: none"> - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - abscess) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c; skin, subcutis - mass d) - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - dilatation, gland/lumen, minimal
1438	S	Macroscopic all tissues	<ul style="list-style-type: none"> - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1438	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
		kidneys	- mineralization, pelvic, bilateral, minimal
		liver	- mineralization, tubular, unilateral, minimal
		lung	- focus of cellular alteration, basophilic, minimal
		pancreas	- hyperplasia, bile duct, minimal
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1439	E	Macroscopic large intestine, cecum	- focus/foci, red, mucosa, mild
		lymph node, mandibular	- discoloration, red, bilateral, mild
		pituitary gland	- enlarged, red, severe
1439	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild
			- hyperplasia, focal medullary, unilateral, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1439	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - carcinoma, pars distalis, malignant, secondary - compression, ventral (pituitary tumor), moderate - hemorrhage, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - nephropathy, chronic progressive, unilateral, minimal - pyelitis, bilateral, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1439	E	Microscopic large intestine, cecum	- erosion/ulcer, moderate corresponds to macroscopic observation (large intestine, cecum - focus/foci, red)
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hyperplasia, bile duct, minimal
		lung	- inflammation, subacute/chronic, minimal
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, mild corresponds to macroscopic observation (lymph node, mandibular - discoloration, red)
		lymph node, mesenteric	- within normal limits
		mammary gland	- fibroadenoma, benign, primary, incidental, not cause of death slide 18.
		nerve, sciatic	- hyperplasia, lobular, mild
		nose, level a	- degeneration, axonal/myelin, minimal
		nose, level b	- within normal limits
		nose, level c	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1439	E	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits one of pair present - within normal limits - carcinoma, pars distalis, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1439	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1440	S	Macroscopic lymph node, iliac	- not identified, bilateral, no grade draining node for mass a. draining node for mass b, right.
		skin, subcutis	- mass, tan, mass a, anogenital region, present corresponds to antemortem observation (mass 1) approximately 7.0 x 7.5 x 2.5 cm. - mass, tan, mass b, right inguinal area, present approximately 2.5 x 2.0 x 1.0 cm.
1440	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, mild one of pair present
		kidneys	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1440	S	Microscopic liver	- focus of cellular alteration, basophilic, minimal - focus of cellular alteration, clear, minimal - focus of cellular alteration, eosinophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal
		lung	- histiocytosis, alveolar, minimal
		mammary gland	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		pancreas	- atrophy, acinar, minimal
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- polyp, stromal, benign, primary, incidental, not cause of death
1441	E	Macroscopic pituitary gland	- enlarged, red, severe
1441	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1441	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - atrophy, unilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1441	E	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1441	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1441	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - pituitary tumor
1442	E	Macroscopic lymph node, axillary lymph node, inguinal pituitary gland	- within normal limits draining node for mass b, left. - not identified, right, no grade draining node for mass a. - enlarged, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1442	E	Macroscopic skin, subcutis	- mass, red, mass b, left axillary area, present approximately 1.5 cm in diameter. - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 13.0 cm in diameter. - enlarged, horn, mild
1442	E	uterus with cervix Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal cortical, unilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1442	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1442	E	Microscopic mammary gland	- adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, unilateral, minimal
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	one of pair present - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1442	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1442	E	Microscopic thymus	- depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, moderate corresponds to macroscopic observation (uterus with cervix - enlarged)
		vagina	- within normal limits
		Cause of Death	- mammary tumor
1443	E	Macroscopic adrenal glands	- enlarged, left, moderate
		lymph node, axillary	- within normal limits draining node for mass a, left.
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1443	E	Macroscopic lymph node, inguinal ovaries skin, subcutis	<ul style="list-style-type: none"> - within normal limits draining node for mass b, left. draining node for mass c, right. - cyst, clear, right, mild - mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 10.0 x 6.0 x 4.5 cm. - mass, tan, mass b, left inguinal area, present approximately 2.0 x 2.0 x 1.0 cm. - mass, tan, mass c, anogenital region, present corresponds to antemortem observation (swelling) approximately 3.5 x 2.5 x 1.5 cm.
1443	E	Microscopic adrenal glands aorta	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, unilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - hyperplasia, focal cortical, unilateral, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1443	E	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - cyst, unilateral, minimal - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1443	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1443	E	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, mild corresponds to macroscopic observation (ovaries - cyst) - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1443	E	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1444	E	Macroscopic lymph node, iliac spleen tail	- within normal limits draining node for mass a, bilateral. - enlarged, minimal - mass, ulcerated, mass a, distal tail, present corresponds to antemortem observation (scabbed area nodule) approximately 2.5 x 2.0 x 0.5 cm, tan.
1444	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- within normal limits - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1444	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, iliac lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, mild - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1444	E	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin skin, subcutis small intestine, duodenum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - schwannoma, malignant, primary, mortality-independent corresponds to macroscopic observation (tail - mass a) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1444	E	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, moderate corresponds to macroscopic observation (spleen - enlarged) - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - schwannoma

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1445	E	Macroscopic pituitary gland	- enlarged, moderate
1445	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- hyperplasia, focal cortical, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1445	E	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d	- mineralization, pelvic, bilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, mild - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1445	E	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1445	E	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hyperplasia, epithelial, nonglandular, mild - inflammation, minimal - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1446	D	Macroscopic pituitary gland	- enlarged, mild
1446	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild

E - Euthanized *in extremis*
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1446	D	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1446	D	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- within normal limits - within normal limits - foreign material, moderate plant. - mucus increased, mild - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - foreign material, mild plant. - mucus increased, mild - within normal limits - within normal limits - adenoma, benign, primary, incidental, not cause of death slide 18. - within normal limits - within normal limits - foreign material, minimal plant. - mucus increased, minimal
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1446	D	Microscopic nose, level c	- foreign material, minimal plant.
		nose, level d	- foreign material, minimal plant.
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- adenoma, benign, unilateral, primary, incidental, not cause of death
		pharynx	- within normal limits
		pituitary gland	- hyperplasia, diffuse, pars distalis, mild corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1446	D	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - aspiration of foreign material
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1447	S	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland skin, subcutis	<ul style="list-style-type: none"> - not identified, left, no grade draining node for mass a and mass b. - within normal limits draining node for mass c, left. - enlarged, red, severe - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 2.0 x 1.5 x 0.5 cm. - mass, tan, mass b, left anogenital region, present corresponds to antemortem observation (nodule swelling) approximately 2.5 cm in diameter. - mass, tan, mass c, left lateral neck, present approximately 3.0 cm in diameter.
1447	S	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1447	S	Microscopic kidneys	- mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild - pyelitis, unilateral, minimal
		liver	- infiltration, mononuclear cell, minimal - multinucleated, hepatocytes, minimal - vacuolation, periportal, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- within normal limits
		mammary gland	- adenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c)
		pancreas	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1447	S	Microscopic tongue	- hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild
		uterus with cervix	- within normal limits
1448	D	Macroscopic cavity, thoracic	- mass, red, mass a, present approximately 1.2 x 1.0 x 0.7 cm. cranial to lungs and attached to the trachea.
		lymph node, mandibular	- enlarged, red, left, mild
		lymph node, mediastinal	- not identified, no grade draining node for mass a.
		pituitary gland	- enlarged, severe
		skin	- hair sparse, dorsal cervical region, right, mild corresponds to antemortem observation (hair sparse)
1448	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1448	D	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain cavity, thoracic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands	- within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, mild - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - hemorrhage, minimal - inflammation, granulomatous, moderate corresponds to macroscopic observation (cavity, thoracic - mass a) the lesion consists of multiple pyogranulomas with a central colony of bacteria, all walled off by a fibrous wall. most likely secondary to a dosing injury. - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1448	D	Microscopic heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - inflammation, acute, moderate - dilatation, sinus, minimal - hyperplasia, lymphocyte/plasmacyte, medulla, mild corresponds to macroscopic observation (lymph node, mandibular - enlarged) - within normal limits - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1448	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- exudate, nasal passage, mild - exudate, nasal passage, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1448	D	Microscopic skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1448	D	Microscopic Cause of Death	- pituitary tumor
1449	D	Macroscopic lymph node, axillary pituitary gland skin, subcutis	- within normal limits right, draining node for mass a. left, draining node for mass b. - enlarged, red, severe - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 8.0 x 6.0 x 4.0 cm. - mass, tan, mass b, right lateral thorax, present corresponds to antemortem observation (mass 2) approximately 4.5 x 3.5 x 2.0 cm.
1449	D	Microscopic adrenal glands aorta bone marrow, femur	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - hyperplasia, granulocytic, minimal
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1449	D	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	 - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, minimal - fold/rosette, retinal, unilateral, minimal - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1449	D	Microscopic larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- within normal limits - necrosis, focal, minimal - within normal limits - within normal limits - within normal limits - within normal limits - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild - within normal limits - exudate, nasal passage, minimal - exudate, nasal passage, mild - exudate, nasal passage, minimal - exudate, nasal passage, minimal - hyperplasia, sex-cord/stromal, bilateral, mild - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1449	D	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular	- within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1449	D	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- depletion, lymphoid, generalized, moderate - within normal limits - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1450	S	Macroscopic lymph node, axillary ovaries pituitary gland	- within normal limits draining node for mass a, left. - cyst, clear, left, mild - enlarged, red, mild
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1450	S	Macroscopic skin, subcutis	- mass, tan, mass a, left axillary area, present corresponds to antemortem observation (nodule) approximately 2.0 cm in diameter.
1450	S	Microscopic adrenal glands kidneys liver lung lymph node, axillary mammary gland ovaries	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal cortical, unilateral, minimal - mineralization, pelvic, bilateral, mild - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - cyst, unilateral, mild corresponds to macroscopic observation (ovaries - cyst)
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1450	S	Microscopic pancreas pituitary gland stomach, nonglandular tongue uterus with cervix	- adenoma, islet cell, benign, primary, incidental, not cause of death - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits
1451	E	Macroscopic lymph node, axillary lymph node, inguinal ovaries pituitary gland	- not identified, bilateral, no grade draining node for mass a, left and mass c, right. - not identified, right, no grade draining node for mass b. - cyst, clear, right, moderate - enlarged, moderate
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1451	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 0.8 cm in diameter - mass, tan, mass c, right axillary area, present corresponds to antemortem observation (swelling) approximately 0.7 cm in diameter. - mass, ulcerated, mass b, anogenital region, right, present corresponds to antemortem observation (mass 2) approximately 8.0 cm in diameter, tan.
1451	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal cortical, unilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1451	E	Microscopic cavity, abdominal	- mesothelioma, malignant, secondary see kidney (slide 1), adrenal gland (slide 5), pancreas (slide 11), and urinary bladder (slide 17).
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1451	E	Microscopic liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d	- focus of cellular alteration, basophilic, mild - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass c) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, moderate - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1451	E	Microscopic ovaries	- mesothelioma, malignant, bilateral, primary, incidental, not cause of death corresponds to macroscopic observation (ovaries - cyst) one ovary has a small tumor, the other large.
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- degeneration/regeneration, myofiber, minimal
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1451	E	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - erosion/ulcer, minimal - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1451	E	Microscopic Cause of Death	- mammary tumor
1452	E	Macroscopic liver lymph node, axillary lymph node, inguinal pituitary gland skin, subcutis spleen	- discoloration, tan, multiple lobes, mild - within normal limits right is draining node for mass a. - within normal limits right is draining node for mass b. - enlarged, moderate - mass, tan, mass b, right anogenital region, present approximately 2.5 x 2.0 x 1.0 cm. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (scabbed area mass 1) tan, approximately 6.0 x 5.0 x 4.0 cm. - enlarged, mild
1452	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1452	E	Microscopic large intestine, rectum larynx liver lung lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - within normal limits - fibroadenoma, benign, multiple, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) slide 26-2 and slide 18r-1. - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1452	E	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin skin, subcutis small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- within normal limits - atrophy, acinar, minimal - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosarcoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1452	E	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - hematopoiesis, extramedullary, increased, moderate corresponds to macroscopic observation (spleen - enlarged) - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - liver - discoloration, tan - fibrosarcoma/fibroma
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1453	E	Macroscopic lymph node, inguinal	- within normal limits draining node for mass a, left.
		pituitary gland	- enlarged, red, mild
		skin, subcutis	- mass, ulcerated, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 6.0 x 3.0 x 1.0 cm, tan.
1453	E	spleen	- enlarged, moderate
		Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), mild
		esophagus	- within normal limits
		eyes	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1453	E	Microscopic eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrima glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal	- within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - pyelitis, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - necrosis, focal, minimal - histiocytosis, alveolar, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1453	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1453	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild corresponds to macroscopic observation (spleen - enlarged) - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1453	E	Microscopic ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1454	S	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland	- within normal limits draining node for mass a, right. - within normal limits draining node for mass b, left, and mass c, right. - enlarged, severe

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1454	S	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 4.0 x 3.5 x 2.0 cm. - mass, tan, mass b, left lateral neck, present approximately 2.0 x 1.0 x 1.0 cm. - mass, tan, mass c, right lateral neck, present approximately 1.0 x 0.5 x 0.5 cm.
1454	S	Microscopic adrenal glands kidneys liver lung	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - mineralization, pelvic, bilateral, mild - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - necrosis, focal, minimal - vacuolation, centrilobular, minimal - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1454	S	Microscopic lymph node, inguinal lymph node, mandibular mammary gland pancreas pituitary gland stomach, nonglandular tongue uterus with cervix	- within normal limits - within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c) - fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) - atrophy, acinar, minimal - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits
1455	D	Macroscopic pituitary gland	- enlarged, red, moderate
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1455	D	Macroscopic skin	- abrasion/scab, sacral, mild
1455	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate - hemorrhage, minimal
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
			one of pair present
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1455	D	Microscopic heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - vacuolation, periportal, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1455	D	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, epidermal, mild corresponds to macroscopic observation (skin - abrasion/scab) - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1455	D	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1456	D	Macroscopic lymph node, axillary	- within normal limits left is draining node for mass a.
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1456	D	Macroscopic pituitary gland skin, subcutis	<ul style="list-style-type: none"> - enlarged, tan, moderate - mass, tan, mass a, ventral neck, present corresponds to antemortem observation (mass 1 scabbed area cannibalized/partially cannibalized) approximately 10.0 x 8.0 x 3.0 cm and appears to be partially cannibalized. extends from left lateral neck to right ventral axillary area and engulfs left forelimb.
1456	D	spleen Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	<ul style="list-style-type: none"> - enlarged, mild - adenoma, cortical, benign, unilateral, primary, incidental, not cause of death - angiectasis/cystic degeneration, focal cortical, bilateral, mild - hematopoiesis, extramedullary, bilateral, mild - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, mild - within normal limits - within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1456	D	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - not examined autolysis too severe for diagnosis - within normal limits - within normal limits - cardiomyopathy, moderate - within normal limits - mineralization, tubular, bilateral, mild - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1456	D	Microscopic liver	- hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, mild - infiltration, mononuclear cell, minimal - leukocytosis, sinusoidal, mild - necrosis, moderate
		lung	- histiocytosis, alveolar, minimal - leukocytosis, vascular, mild
		lymph node, axillary	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) slide 18 and 26-1, 26-1a, 26-1b. - hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1456	D	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1456	D	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - hematopoiesis, extramedullary, increased, moderate corresponds to macroscopic observation (spleen - enlarged) - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1457	E	Macroscopic brain ovaries	- focus/foci, black, focal, cerebrum, mild - cyst, clear, right, mild

E - Euthanized *in extremis*

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1457	E	Macroscopic oviducts pituitary gland	- cyst, clear, right, mild - enlarged, red, moderate
1457	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - carcinoma, pars distalis, malignant, secondary corresponds to macroscopic observation (brain - focus/foci, black) - compression, ventral (pituitary tumor), moderate - hemorrhage, moderate corresponds to macroscopic observation (brain - focus/foci, black) - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1457	E	Microscopic eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - within normal limits - within normal limits - hyperplasia, focal, unilateral, minimal - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1457	E	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- within normal limits - within normal limits - exudate, nasal passage, minimal - foreign material, minimal plant. - within normal limits - within normal limits - cyst, unilateral, mild corresponds to macroscopic observation (ovaries - cyst) - within normal limits - atrophy, acinar, minimal - within normal limits - within normal limits - carcinoma, pars distalis, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1457	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, epithelial, nonglandular, moderate - inflammation, mild - hyperplasia, lymphoid, medulla, mild - hyperplasia, c-cell, focal, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1457	E	Microscopic uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - oviducts - cyst - pituitary tumor
1458	E	Macroscopic pituitary gland thymus	- enlarged, red, mild - discoloration, red, mild
1458	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1458	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1458	E	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1458	E	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - thymus - discoloration, red - pituitary tumor
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1459	E	Macroscopic pituitary gland	- enlarged, red, severe
1459	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal medullary, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1459	E	Microscopic joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - infiltration, mononuclear cell, minimal - necrosis, focal, mild - vacuolation, periportal, mild - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - hyperplasia, lobular, moderate - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1459	E	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1459	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - edema, mild - hyperplasia, epithelial, nonglandular, mild - depletion, lymphoid, generalized, severe - hyperplasia, c-cell, focal, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - granular cell tumor, benign, primary, incidental, not cause of death - pituitary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1460	S	Macroscopic adrenal glands lymph node, axillary mammary gland pituitary gland skin, subcutis	- enlarged, red, right, mild - not identified, right, no grade draining node for mass a. - swollen/thickened, tan, generalized, mild - enlarged, red, mild - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (hair sparse mass 1) approximately 3.0 cm in diameter.
1460	S	Microscopic adrenal glands kidneys liver lung	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged) - hyperplasia, tubular, unilateral, minimal - mineralization, pelvic, bilateral, minimal - hematopoiesis, extramedullary, minimal - vacuolation, focal, minimal - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1460	S	Microscopic mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened)
		pancreas	- atrophy, acinar, mild
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, minimal
1461	E	Macroscopic lymph node, axillary	- within normal limits draining node for mass a, left.

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1461	E	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits draining node for mass b, left. draining node for mass c, right. - within normal limits draining node for mass d, right. - enlarged, moderate - mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 5.0 x 2.5 x 2.5 cm. - mass, tan, mass b, left inguinal area, present corresponds to antemortem observation (mass 2) approximately 2.0 cm in diameter. - mass, tan, mass d, right lateral neck, present approximately 1.0 cm in diameter. - mass, ulcerated, mass c, right inguinal area, present corresponds to antemortem observation (mass 3) approximately 1.5 cm in diameter, tan.
1461	E	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1461	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	- within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1461	E	Microscopic large intestine, rectum larynx liver lung lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal - histiocytosis, sinus, mild - within normal limits right inguinal not examined, misidentified tissue. - erythrocytosis/erythrophagocytosis, sinus, mild - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1461	E	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass c; skin, subcutis - mass d) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1461	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1461	E	Microscopic thymus	- depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- mammary tumor
1462	E	Macroscopic lymph node, inguinal	- within normal limits draining node for mass a, left.
		pituitary gland	- enlarged, red, severe
		skin, subcutis	- mass, tan, mass a, left inguinal area, present approximately 2.5 x 2.0 x 1.0 cm.

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1462	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, tubular, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1462	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - within normal limits - within normal limits - foreign material, minimal plant material. - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1462	E	Microscopic pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	- within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1462	E	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1463	E	Macroscopic lymph node, inguinal pituitary gland	- not identified, left, no grade draining node for mass a. - enlarged, severe
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1463	E	Macroscopic skin, subcutis	- mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 9.0 cm in diameter.
1463	E	Microscopic adrenal glands	- adenoma, cortical, benign, unilateral, primary, incidental, not cause of death - angiectasis/cystic degeneration, focal cortical, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), minimal
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1463	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a	- within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - histiocytosis, alveolar, minimal - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1463	E	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - hyperplasia, focal, bilateral, mild - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1463	E	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - pituitary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1464	D	Macroscopic adipose tissue	- discoloration, red, mild white adipose near spleen.
		adrenal glands	- enlarged, right, mild
		liver	- focus/foci, tan, multiple lobes, mild
		lymph node, axillary	- within normal limits draining node for mass a, right.
		lymph node, inguinal	- not identified, right, no grade draining node for mass b.
		skin, subcutis	- mass, black, mass b, right inguinal area, present corresponds to antemortem observation (mass 2) approximately 4.0 x 3.0 x 1.5 cm.
			- mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 2.0 x 2.0 x 1.0 cm.
			- focus/foci, black, horn, minimal
1464	D	uterus with cervix Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged) - hyperplasia, focal medullary, bilateral, minimal
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1464	D	Microscopic	
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal - thrombus, severe
		joint, tibiofemoral	- within normal limits
		kidneys	- dilatation, tubular, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1464	D	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - necrosis, hepatocytes, centrilobular, severe corresponds to macroscopic observation (liver - focus/foci, tan) - vacuolation, median cleft, mild - vacuolation, periportal, mild - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1464	D	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		mesentery/peritoneum	- galactoceles, mild - hyperplasia, lobular, mild - congestion, mild corresponds to macroscopic observation (adipose tissue - discoloration, red)
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, bilateral, minimal
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1464	D	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1464	D	Microscopic tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - uterus with cervix - focus/foci, black - heart failure/atrial thrombus
1465	D	Macroscopic lymph node, iliac pituitary gland urinary bladder uterus with cervix	- within normal limits draining node for mass a, bilateral. - enlarged, severe - within normal limits the bladder is encompassed with mass a. - enlarged, body, moderate - mass, brown, mass a, body, present approximately 7.0 x 4.0 x 5.0 cm.
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1465	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- hyperplasia, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - not examined autolysis too severe for diagnosis - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1465	D	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, iliac lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1465	D	Microscopic pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	- atrophy, acinar, minimal - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, moderate
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1465	D	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - not examined - leiomyosarcoma, malignant, secondary - leiomyosarcoma, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (uterus with cervix - enlarged; uterus with cervix - mass a) slide 16-1, 16-1a, 16-1b, and 16-1c. - polyp, glandular, benign, primary, incidental, not cause of death slide 16. - within normal limits - uterus tumor
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1466	D	Macroscopic mammary gland pituitary gland	- swollen/thickened, generalized, mild - enlarged, mild
1466	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1466	D	Microscopic joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal corresponds to macroscopic observation (mammary gland - swollen/thickened) - within normal limits - within normal limits - within normal limits - within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1466	D	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Terminal

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1467	S	Macroscopic lymph node, inguinal skin, subcutis	<ul style="list-style-type: none"> - within normal limits draining node for mass a and mass d, right. draining node for mass c, left. - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 5.0 x 4.0 x 2.0 cm. - mass, tan, mass b, left axillary area, present corresponds to antemortem observation (mass 2) approximately 4.0 x 2.5 x 2.0 cm. - mass, tan, mass c, left inguinal area, present corresponds to antemortem observation (mass 3) approximately 3.0 x 3.0 x 1.5 cm. - mass, tan, mass d, right anogenital region, present corresponds to antemortem observation (mass 4) approximately 6.0 x 4.5 x 3.0 cm. - enlarged, horn, mild
1467	S	uterus with cervix Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate

S - Scheduled necropsy

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1467	S	Microscopic kidneys	- hydronephrosis, bilateral, mild - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal
		liver	- hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal
		lung	- within normal limits
		lymph node, axillary	- within normal limits
		lymph node, inguinal	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass c) two separate tumors present (collision tumor). - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c; skin, subcutis - mass d)
		pancreas	- hyperplasia, islet cell, mild
		stomach, nonglandular	- within normal limits
		tongue	- hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1467	S	Microscopic uterus with cervix	- dilatation, gland/lumen, moderate corresponds to macroscopic observation (uterus with cervix - enlarged)
1468	D	Macroscopic animal/whole body	- body fat depleted, moderate corresponds to antemortem observation (thin)
1468	D	pituitary gland Microscopic adrenal glands	- enlarged, severe - angiectasis/cystic degeneration, focal cortical, bilateral, moderate - hyperplasia, focal medullary, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits

S - Scheduled necropsy
D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1468	D	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hydronephrosis, unilateral, mild - hyperplasia, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1468	D	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1468	D	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1468	D	Microscopic urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - dilatation, gland/lumen, minimal - hyperplasia, cervical fibromuscular, mild - within normal limits - pituitary tumor
1469	S	Macroscopic pituitary gland uterus with cervix	- enlarged, moderate - enlarged, cervix, moderate
1469	S	Microscopic adrenal glands kidneys liver lung pancreas	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal cortical, unilateral, minimal - nephropathy, chronic progressive, bilateral, moderate - focus of cellular alteration, eosinophilic, minimal - histiocytosis, alveolar, minimal - atrophy, acinar, minimal - hyperplasia, islet cell, mild
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1469	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild - hyperplasia, cervical fibromuscular, moderate corresponds to macroscopic observation (uterus with cervix - enlarged)
1470	E	Macroscopic lymph node, axillary	- hyperplasia, squamous cell, mild - within normal limits draining node for mass a, right and draining node for mass c, left.
		lymph node, inguinal	- within normal limits draining node for mass b, left.

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1470	E	Macroscopic pituitary gland skin, subcutis	<ul style="list-style-type: none"> - enlarged, mild - mass, tan, mass b, left inguinal area, present corresponds to antemortem observation (swelling) approximately 1.7 x 0.8 x 0.4 cm in size. - mass, tan, mass c, left axillary area, present approximately 1.2 x 1.5 x 0.4 cm in size. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 5.7 x 2.1 x 1.4 cm in size, tan.
1470	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal cortical, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1470	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1470	E	Microscopic lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits one of pair present - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1470	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1470	E	Microscopic thymus	- depletion, lymphoid, generalized, severe
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- mammary tumor
1471	S	Macroscopic pituitary gland	- enlarged, severe
1471	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
			- hyperplasia, focal cortical, unilateral, minimal

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1471	S	Microscopic kidneys	<ul style="list-style-type: none"> - edema, papilla, bilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal
		liver	<ul style="list-style-type: none"> - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal
		lung	<ul style="list-style-type: none"> - within normal limits
		pancreas	<ul style="list-style-type: none"> - atrophy, acinar, minimal
		pituitary gland	<ul style="list-style-type: none"> - adenoma, pars distalis, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	<ul style="list-style-type: none"> - within normal limits
		tongue	<ul style="list-style-type: none"> - within normal limits
		uterus with cervix	<ul style="list-style-type: none"> - dilatation, gland/lumen, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1472	E	Macroscopic liver lymph node, inguinal pituitary gland skin, subcutis	- cyst, clear, left lateral lobe, moderate approximately 1.5 cm in diameter. - within normal limits right is draining node for mass a. - enlarged, red, severe - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 8.0 x 6.0 x 3.8 cm.
1472	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1472	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal	- within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, moderate - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, biliary, simple, moderate corresponds to macroscopic observation (liver - cyst) - infiltration, mononuclear cell, minimal - vacuolation, periportal, mild - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1472	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- within normal limits - within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1472	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- atrophy, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1472	E	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - pituitary tumor
1473	E	Macroscopic lymph node, mandibular mammary gland pituitary gland skin, subcutis	- within normal limits draining node for mass a, left. - swollen/thickened, tan, generalized, moderate - enlarged, red, mild - mass, ulcerated, mass a, cervical, left, present corresponds to antemortem observation (mass 1 hair sparse mass 2) approximately 5.0 cm in diameter, tan.
1473	E	Microscopic adrenal glands aorta	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate - hyperplasia, focal cortical, unilateral, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1473	E	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, transitional cell, unilateral, mild - infarct, unilateral, minimal - mineralization, tubular, bilateral, minimal - pyelitis, unilateral, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1473	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d	- within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1473	E	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1473	E	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - within normal limits - mammary tumor
1474	E	Macroscopic pituitary gland	- enlarged, severe

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1474	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1474	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, mild - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1474	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1474	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1475	S	Macroscopic lymph node, inguinal pituitary gland skin, subcutis uterus with cervix	- within normal limits draining node for mass a, right. - enlarged, red, severe - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1 skin discolored) approximately 1.0 x 2.0 x 1.0 cm, surrounded by fluid filled cyst that ruptured. - enlarged, horn, minimal

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1475	S	Microscopic adrenal glands kidneys liver lung lymph node, inguinal mammary gland pancreas pituitary gland stomach, nonglandular tongue uterus with cervix	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - hematopoiesis, extramedullary, minimal - histiocytosis, alveolar, minimal - within normal limits - adenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged)
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1476	D	Macroscopic adrenal glands kidneys lymph node, iliac skin, subcutis	- enlarged, left, mild - dilatation, pelvic, bilateral, mild - enlarged, right, mild draining node for mass b. - mass, ulcerated, mass b, anogenital region, present corresponds to antemortem observation (mass 2) approximately 6.0 cm in diameter, tan. - distended with urine, red, severe
1476	D	urinary bladder Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged) - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, mild - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1476	D	Microscopic brain clitoral glands esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- within normal limits - carcinoma, squamous cell, malignant, unilateral, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, mild - within normal limits - dilatation, tubular, bilateral, mild - hydronephrosis, bilateral, mild corresponds to macroscopic observation (kidneys - dilatation, pelvic) - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1476	D	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, iliac lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts	- within normal limits - within normal limits - within normal limits - within normal limits - vacuolation, periportal, minimal - within normal limits - hyperplasia, lymphocyte/plasmacyte, medulla, mild corresponds to macroscopic observation (lymph node, iliac - enlarged) - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1476	D	Microscopic pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular	- within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1476	D	Microscopic stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	<ul style="list-style-type: none"> - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - dilatation, bilateral, moderate - dilatation, moderate - corresponds to macroscopic observation (urinary bladder - distended with urine) - hemorrhage, severe - corresponds to macroscopic observation (urinary bladder - distended with urine) - hyperplasia, simple transitional cell, mild - inflammation, moderate - dilatation, gland/lumen, minimal - within normal limits - clitoral gland tumor
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u>			
1477	E	Macroscopic pituitary gland	- enlarged, red, severe
1477	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1477	E	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - vacuolation, periportal, mild - within normal limits - erythrocytosis/erythrophagocytosis, sinus, mild - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1477	E	Microscopic pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	- within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1477	E	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, lymphoid, medulla, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1478	E	Macroscopic lymph node, axillary	- within normal limits left is draining node for mass a, right is draining node for mass b.

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1478	E	Macroscopic pituitary gland skin, subcutis	<ul style="list-style-type: none"> - enlarged, red, severe - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (mass 2) approximately 4.0 x 3.4 x 2.0 cm. - mass, ulcerated, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 4.5 x 3.0 x 2.2 cm. tan in color.
1478	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1478	E	Microscopic eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - within normal limits - hyperplasia, lymphocyte/plasmacyte, medulla, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1478	E	Microscopic mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, bilateral, mild
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1478	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - hyperplasia, lymphoid, medulla, mild - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1478	E	Microscopic ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - dilatation, gland/lumen, mild - within normal limits - mammary tumor
1479	E	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland skin, subcutis	- within normal limits draining node for mass a, left. - within normal limits draining node for mass b, bilateral. - enlarged, red, mild - mass, red, mass b, ventral thorax, present corresponds to antemortem observation (nodule) approximately 1.5 cm in diameter. - mass, ulcerated, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 2.0 cm in diameter, red.

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1479	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), minimal
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1479	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a	- within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, mild - within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - inflammation, subacute/chronic, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1479	E	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1479	E	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, mild - hyperplasia, epithelial cell, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1480	E	Macroscopic ovaries pituitary gland uterus with cervix	- cyst, red, right, moderate - enlarged, severe - enlarged, body, mild
1480	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1480	E	Microscopic heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d	- within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - pyelitis, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1480	E	Microscopic ovaries	- cyst, unilateral, moderate corresponds to macroscopic observation (ovaries - cyst) - luteoma, benign, unilateral, primary, incidental, not cause of death
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>1 mg/kg/day</u> 1480	E	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, cervical fibromuscular, moderate corresponds to macroscopic observation (uterus with cervix - enlarged) - within normal limits - pituitary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1491	S	Macroscopic lymph node, inguinal	- not identified, left, no grade draining node for mass a.
		pituitary gland	- enlarged, moderate
		skin, subcutis	- mass, ulcerated, mass a, left inguinal area, present corresponds to antemortem observation (abrasion(s) mass 1) approximately 4.0 x 3.0 x 1.0 cm, tan.
1491	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal
		kidneys	- hyperplasia, focal medullary, unilateral, minimal
			- mineralization, pelvic, bilateral, minimal
			- nephropathy, chronic progressive, bilateral, minimal
		liver	- angiectasis, mild
			- focus of cellular alteration, basophilic, minimal
		lung	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		pancreas	- atrophy, acinar, minimal
			- hyperplasia, islet cell, minimal
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1491	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1492	E	Macroscopic pituitary gland	- enlarged, red, severe
1492	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1492	E	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, bilateral, minimal - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1492	E	Microscopic liver	- focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - vacuolation, periportal, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	one of pair present - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1492	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1492	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1493	D	Macroscopic liver lymph node, inguinal pituitary gland skin skin, subcutis	- focus/foci, red, multiple lobes, mild - not identified, left, no grade draining node for mass a. - enlarged, red, severe - hair sparse, ventral thorax, head, mild corresponds to antemortem observation (hair sparse) - mass, tan, mass a, left inguinal area, present approximately 1.0 x 1.0 x 0.5 cm.
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1493	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1493	D	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d	- within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal - within normal limits slide 26-1. - within normal limits - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1493	D	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1493	D	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - liver - focus/foci, red - pituitary tumor
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1494	E	Macroscopic liver ovaries pituitary gland uterus with cervix	- focus/foci, red, right lateral lobe, minimal - cyst, clear, left, mild - enlarged, red, severe - enlarged, horn, mild
1494	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1494	E	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric	- within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - angiectasis, mild corresponds to macroscopic observation (liver - focus/foci, red) - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, mild - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1494	E	Microscopic mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual	- hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal corresponds to macroscopic observation (ovaries - cyst) - within normal limits - dilatation, duct, mild - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1494	E	Microscopic skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, epithelial, nonglandular, moderate - inflammation, mild - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1494	E	Microscopic uterus with cervix	<ul style="list-style-type: none"> - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged) - polyp, stromal, benign, primary, incidental, not cause of death corresponds to macroscopic observation (uterus with cervix - enlarged)
1495	E	vagina Cause of Death Macroscopic adrenal glands lymph node, axillary pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits - pituitary tumor - irregular surface, cystic, bilateral, moderate - within normal limits draining node for mass a, right. - enlarged, red, severe - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (nodule) approximately 2.0 cm in diameter.

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1495	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - irregular surface)
		aorta	- hyperplasia, focal cortical, unilateral, minimal
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1495	E	Microscopic kidneys	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, moderate
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - infiltration, mononuclear cell, minimal - vacuolation, periportal, minimal
		lung	- within normal limits
		lymph node, axillary	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1495	E	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1495	E	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - erosion/ulcer, moderate - inflammation, moderate - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1496	S	Macroscopic adrenal glands mammary gland pituitary gland	- enlarged, right, mild - swollen/thickened, tan, generalized, mild - enlarged, red, mild
1496	S	Microscopic adrenal glands kidneys liver lung mammary gland pancreas	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged) - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - pyelitis, unilateral, minimal - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal - within normal limits - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1496	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1497	E	Macroscopic lymph node, inguinal	- within normal limits draining node for mass a, left.
		pituitary gland	- enlarged, severe
		skin, subcutis	- mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 4.5 x 2.5 x 2.5 cm.
1497	E	Microscopic adrenal glands	- within normal limits

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1497	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1497	E	Microscopic larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - focus of cellular alteration, eosinophilic, mild - within normal limits - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1497	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1497	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - within normal limits - pituitary tumor
1498	E	Macroscopic pituitary gland skin	- enlarged, severe - hair sparse, left foreleg/limb, right foreleg/limb, mild corresponds to antemortem observation (hair sparse)
1498	E	Microscopic adrenal glands aorta bone marrow, femur	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1498	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	 - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - pyelitis, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1498	E	Microscopic liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- within normal limits - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1498	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1498	E	Microscopic urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - pituitary tumor
1499	E	Macroscopic adrenal glands liver lymph node, axillary lymph node, mandibular pituitary gland	- enlarged, bilateral, mild - focus/foci, tan, left lateral lobe, mild - not identified, left, no grade draining node for mass b. - within normal limits draining node for mass a, left. - enlarged, red, moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1499	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, left lateral neck, present corresponds to antemortem observation (mass 1) approximately 8.0 x 6.0 x 4.0 cm. - mass, tan, mass b, left axillary area, present corresponds to antemortem observation (mass 2) approximately 11.5 x 10.0 x 4.0 cm. - small, moderate
1499	E	thymus Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1499	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1499	E	Microscopic liver	<ul style="list-style-type: none"> - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - necrosis, focal, mild
			corresponds to macroscopic observation (liver - focus/foci, tan)
		lung	<ul style="list-style-type: none"> - histiocytosis, alveolar, minimal
		lymph node, mandibular	<ul style="list-style-type: none"> - within normal limits
		lymph node, mesenteric	<ul style="list-style-type: none"> - within normal limits
		mammary gland	<ul style="list-style-type: none"> - fibroadenoma, benign, multiple, primary, mortality-independent
			corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		nerve, sciatic	<ul style="list-style-type: none"> - degeneration, axonal/myelin, minimal
		nose, level a	<ul style="list-style-type: none"> - within normal limits
		nose, level b	<ul style="list-style-type: none"> - within normal limits
		nose, level c	<ul style="list-style-type: none"> - within normal limits
		nose, level d	<ul style="list-style-type: none"> - within normal limits
		ovaries	<ul style="list-style-type: none"> - within normal limits
		oviducts	<ul style="list-style-type: none"> - within normal limits
		pancreas	<ul style="list-style-type: none"> - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1499	E	Microscopic parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular	- within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1499	E	Microscopic stomach, nonglandular thymus	- within normal limits - depletion, lymphoid, generalized, moderate corresponds to macroscopic observation (thymus - small) - hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits one of pair present
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, minimal
		vagina	- within normal limits
		Cause of Death	- mammary tumor
1500	S	Macroscopic pituitary gland	- enlarged, moderate
1500	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal

S - Scheduled necropsy
E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1500	S	Microscopic kidneys	<ul style="list-style-type: none"> - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - pyelitis, bilateral, minimal
		liver	<ul style="list-style-type: none"> - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, clear, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - vacuolation, periportal, minimal
		lung	<ul style="list-style-type: none"> - histiocytosis, alveolar, minimal - inflammation, subacute/chronic, minimal
		pancreas	<ul style="list-style-type: none"> - hyperplasia, acinar cell, focal, minimal
		pituitary gland	<ul style="list-style-type: none"> - adenoma, pars distalis, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	<ul style="list-style-type: none"> - within normal limits
		tongue	<ul style="list-style-type: none"> - within normal limits
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1500	S	Microscopic uterus with cervix	- dilatation, gland/lumen, minimal
1501	D	Macroscopic lymph node, inguinal pituitary gland skin, subcutis	- not identified, left, no grade draining node for mass a. - enlarged, severe - mass, tan, mass a, anogenital region, present corresponds to antemortem observation (swelling) approximately 1.5 x 1.5 x 1.0 cm.
1501	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1501	D	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - not examined autolysis too severe for diagnosis - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1501	D	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- within normal limits - within normal limits - adenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1501	D	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, epithelial, nonglandular, mild - inflammation, mild - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1501	D	Microscopic urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - pituitary tumor
1502	E	Macroscopic liver lymph node, axillary lymph node, iliac pituitary gland skin, subcutis	- focus/foci, red, multiple lobes, mild - not identified, right, no grade draining node for mass b. - within normal limits draining node for mass a, left. - enlarged, severe - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter. - mass, ulcerated, mass b, right axillary area, present corresponds to antemortem observation (mass 2) approximately 3.0 cm in diameter, tan.

E - Euthanized *in extremis*

D - Died on Study

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1502	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1502	E	Microscopic kidneys	<ul style="list-style-type: none"> - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - pyelitis, unilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - dilatation, sinusoidal, minimal - corresponds to macroscopic observation (liver - focus/foci, red) - focus of cellular alteration, basophilic, mild
		lung	- within normal limits
		lymph node, iliac	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1502	E	Microscopic mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, unilateral, minimal - hyperplasia, sex-cord/stromal, unilateral, minimal
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1502	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, c-cell, focal, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1502	E	Microscopic uterus with cervix vagina Cause of Death	- dilatation, gland/lumen, minimal - within normal limits - mammary tumor
1503	E	Macroscopic pituitary gland uterus with cervix	- enlarged, moderate - enlarged, focal, horn, mild
1503	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - hyperplasia, focal cortical, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1503	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1503	E	Microscopic mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, bilateral, mild - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1503	E	Microscopic skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1503	E	Microscopic Cause of Death	- pituitary tumor
1504	E	Macroscopic pituitary gland	- enlarged, red, severe
1504	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1504	E	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- hyperplasia, focal, unilateral, minimal - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1504	E	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1504	E	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - granular cell tumor, benign, primary, incidental, not cause of death - within normal limits - pituitary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1505	E	Macroscopic adrenal glands harderian glands lymph node, axillary lymph node, inguinal skin, subcutis	<ul style="list-style-type: none"> - enlarged, bilateral, mild - discoloration, tan, left, moderate corresponds to antemortem observation (eye protruding) - within normal limits draining node for mass b, right. - not identified, right, no grade draining node for mass a. - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 6.5 x 7.0 x 3.0 cm. - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (mass 2) approximately 3.5 x 2.5 x 15 cm.
1505	E	thymus uterus with cervix Microscopic adrenal glands	<ul style="list-style-type: none"> - discoloration, red, mild - enlarged, minimal - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged) - hyperplasia, focal cortical, unilateral, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1505	E	Microscopic aorta bone bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart	- within normal limits - osteosarcoma, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (harderian glands - discoloration, tan) tumor extends from upper jaw to the back of the eye socket causing the eye to protrude. see slides 14-1, 14-1 r-1, 24 and 25. - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - inflammation, acute, unilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1505	E	Microscopic joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland multicentric neoplasm nerve, sciatic	- within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal - histiocytosis, sinus, mild - within normal limits - within normal limits - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, minimal - lymphoma, malignant, multicentric, incidental, not cause of death - degeneration, axonal/myelin, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1505	E	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - hyperplasia, diffuse, pars distalis, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1505	E	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - lymphoma, malignant, multicentric, incidental, not cause of death corresponds to macroscopic observation (thymus - discoloration, red) - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged) - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1505	E	Microscopic Cause of Death	- bone tumor
1506	D	Macroscopic lymph node, inguinal skin, subcutis	- not identified, right, no grade draining node for mass a. - mass, ulcerated, mass a, right inguinal area, present corresponds to antemortem observation (mass 1 cannibalized/partially cannibalized) approximately 9.0 x 6.0 x 3.0 cm, tan.
1506	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1506	D	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - necrosis, hepatocytes, centrilobular, moderate - histiocytosis, alveolar, minimal - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1506	D	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1506	D	Microscopic skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1507	E	Macroscopic pituitary gland	- enlarged, red, severe
1507	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1507	E	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1507	E	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	- within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1507	E	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hyperplasia, epithelial, nonglandular, moderate - inflammation, mild - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1508	E	Macroscopic lymph node, axillary	- not identified, right, no grade draining node for mass a.
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1508	E	Macroscopic lymph node, mediastinal	- within normal limits draining node for mass b.
		skin, subcutis	- mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 10.0 x 7.0 x 4.0 cm.
		thymus	- mass, tan, mass b, present approximately 2.5 x 2.0 x 0.5 cm.
1508	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - hyperplasia, focal medullary, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1508	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - infiltration, mononuclear cell, minimal - necrosis, focal, minimal - vacuolation, periportal, minimal
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1508	E	Microscopic lung lymph node, mandibular lymph node, mediastinal lymph node, mesenteric mammary gland multicentric neoplasm nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - lymphoma, malignant, multicentric, incidental, not cause of death - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - polyarteritis, moderate - not examined - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1508	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- lymphoma, malignant, multicentric, incidental, not cause of death corresponds to macroscopic observation (thymus - mass b)
		thyroid gland	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1508	E	Microscopic tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1509	E	Macroscopic adrenal glands lymph node, axillary mammary gland pituitary gland skin, subcutis	- cyst, left, moderate - not identified, right, no grade draining node for mass a. - swollen/thickened, tan, generalized, mild - enlarged, red, mild - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1 hair sparse) approximately 10.0 x 10.0 x 4.0 cm.
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1509	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - cyst)
		aorta	- hyperplasia, focal cortical, unilateral, minimal
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), minimal
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1509	E	Microscopic kidneys	- hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- focus of cellular alteration, basophilic, mild - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, moderate corresponds to macroscopic observation (mammary gland - swollen/thickened)
		nerve, sciatic	- degeneration, axonal/myelin, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1509	E	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - within normal limits - degeneration/necrosis, olfactory epithelium, minimal - hyperplasia, sex-cord/stromal, bilateral, mild - within normal limits - within normal limits - hyperplasia, focal, unilateral, mild one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1509	E	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, moderate - thrombus, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1509	E	Microscopic vagina Cause of Death	- within normal limits - mammary tumor
1510	D	Macroscopic pituitary gland	- enlarged, red, moderate
1510	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1510	D	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1510	D	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1510	D	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, mild - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1511	E	Macroscopic pituitary gland	- cyst, red, moderate
1511	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1511	E	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1511	E	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	- within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - cyst) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1511	E	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1512	D	Macroscopic all tissues	- within normal limits
1512	D	Microscopic adrenal glands	- within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1512	D	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - schwannoma, malignant, primary, fatal, positive cause of death - within normal limits - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1512	D	Microscopic larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	 - within normal limits - necrosis, hepatocytes, centrilobular, severe - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1512	D	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1512	D	Microscopic vagina Cause of Death	- within normal limits - schwannoma
1513	E	Macroscopic all tissues	- within normal limits
1513	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - lymphoma, malignant, multicentric, fatal, positive cause of death - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1513	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland multicentric neoplasm nerve, sciatic nose, level a nose, level b	- within normal limits - within normal limits - within normal limits - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - within normal limits - lymphoma, malignant, multicentric, fatal, positive cause of death

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1513	E	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- lymphoma, malignant, multicentric, fatal, positive cause of death - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - lymphoma, malignant, multicentric, fatal, positive cause of death slide 20 and 21. - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1513	E	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hematopoiesis, extramedullary, increased, moderate - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - metaplasia, squamous, mild - within normal limits - lymphoid tumor
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1514	E	Macroscopic animal/whole body	- body fat depleted, mild corresponds to antemortem observation (thin)
1514	E	pituitary gland Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart	- enlarged, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1514	E	Microscopic joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- within normal limits - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1514	E	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	- within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1514	E	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1515	E	Macroscopic lymph node, mandibular pituitary gland	- within normal limits left, draining node for mass a. - enlarged, red, moderate

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1515	E	Macroscopic skin, subcutis	- mass, ulcerated, mass a, ventral neck, present corresponds to antemortem observation (mass 1) approximately 8.0 x 6.0 x 3.5 cm. mass a extends across left ventral neck and down left forelimb. is tan in color.
1515	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1515	E	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - vacuolation, periportal, minimal - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1515	E	Microscopic mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- adenoma, islet cell, benign, primary, incidental, not cause of death - atrophy, acinar, mild - fibrosis, minimal
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1515	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1515	E	Microscopic uterus with cervix vagina Cause of Death	- dilatation, gland/lumen, minimal - within normal limits - mammary tumor
1516	S	Macroscopic foot/feet lymph node, axillary lymph node, iliac lymph node, inguinal	- ulcer, plantar/palmar, mild corresponds to antemortem observation (ulcer plantar/palmar) - within normal limits draining node for mass a, left. - within normal limits draining node for mass c, bilateral. - not identified, right, no grade draining node for mass b.
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1516	S	Macroscopic skin, subcutis	- mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 2.0 cm in diameter. - mass, tan, mass b, right inguinal area, present corresponds to antemortem observation (mass 2) approximately 2.0 cm in diameter.
		uterus with cervix	- mass, tan, mass c, horn, present corresponds to antemortem observation (swelling) approximately 1.0 cm in diameter.
1516	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, unilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - pyelitis, unilateral, minimal
		kidneys	
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1516	S	Microscopic liver	<ul style="list-style-type: none"> - focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal
		lung	<ul style="list-style-type: none"> - within normal limits
		lymph node, axillary	<ul style="list-style-type: none"> - within normal limits
		lymph node, iliac	<ul style="list-style-type: none"> - dilatation, sinus, minimal
		mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		pancreas	<ul style="list-style-type: none"> - within normal limits
		stomach, nonglandular	<ul style="list-style-type: none"> - within normal limits
		tongue	<ul style="list-style-type: none"> - within normal limits
		uterus with cervix	<ul style="list-style-type: none"> - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (uterus with cervix - mass c) - dilatation, gland/lumen, mild
S - Scheduled necropsy			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1517	E	Macroscopic lymph node, axillary lymph node, inguinal lymph node, mandibular pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits draining node for mass b, right. - not identified, left, no grade draining node for mass c. - discoloration, red, bilateral, mild draining node for mass a, left. - enlarged, severe - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (nodule) approximately 3.0 cm in diameter. - mass, tan, mass c, left inguinal area, present approximately 3.0 cm in diameter. - mass, ulcerated, mass a, left lateral neck, present corresponds to antemortem observation (ulcer mass 1) approximately 6.0 cm in diameter, tan. - enlarged, moderate
1517	E	spleen Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hematopoiesis, extramedullary, bilateral, minimal

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1517	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, mild - pyelitis, bilateral, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1517	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a	- within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - histiocytosis, alveolar, minimal - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal corresponds to macroscopic observation (lymph node, mandibular - discoloration, red) - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass c) - hyperplasia, lobular, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1517	E	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1517	E	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, moderate corresponds to macroscopic observation (spleen - enlarged) - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1518	E	Macroscopic lymph node, axillary pituitary gland skin, subcutis	- within normal limits draining node for mass a, right. - enlarged, mild - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter, tan.
1518	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1518	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - within normal limits - within normal limits - within normal limits - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - within normal limits - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1518	E	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	 - within normal limits
E - Euthanized <i>in extremis</i>			

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1518	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - erosion/ulcer, mild - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary gland - enlarged - mammary tumor

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1519	E	Macroscopic lymph node, axillary lymph node, inguinal pituitary gland skin, subcutis	- within normal limits draining node for mass a, right. - not identified, left, no grade draining node for mass b. - enlarged, red, severe - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 4.0 cm in diameter. - mass, tan, mass b, left inguinal area, present approximately 2.0 cm in diameter.
1519	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1519	E	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary	- compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosis, minimal - necrosis, focal, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1519	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, acinar cell, focal, minimal - within normal limits one of pair present - within normal limits

E - Euthanized *in extremis*

Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1519	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
E - Euthanized <i>in extremis</i>			